Üç Thiazolidine-4-Karboksilik Asit Türevinin *Pseudomonas, Acinetobacter, Staphylococcus Aureus* ve *Escherichia Coli Bakterilerine* Karşı Antibakteriyel Özelliklerinin İncelenmesi

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Öz

Çok ilaca dirençli bakterilerin tedavisi, halk sağlığı için artan bir küresel sorundur. Bu dirence ayak uydurabilmek için yeni ilaç aktif maddelerine ihtiyaç duyulmaktadır. Tiazolidin-4-karboksilik asitlerin (TCA) doğal olarak oluşan amino asitlerin çeşitli esas işlevlerini taklit ederek bakteri gelişimini engelleyebildiği bilinmektedir. Bu nedenle, ikisi yeni olan üç TCA türevinin sentezlenmesi amaçlanmış ve antibakteriyel aktiviteleri çok ilaca dirençli (MDR) bakteriler üzerinde araştırılmıştır. Bileşikler (la-c), L-Sistein hidroklorür ve dihidroksibenzaldehit türevlerinden sentezlendi ve çoklu ilaç dirençli bakterilere karşı *in vitro* aktiviteleri CLSI kriterlerine göre Kirby-Bauer yöntemi ile denendi. 1a-c, mevcut antibiyotiklere kıyasla *S. aureus* gibi Gram pozitif bakterilere ve *Pseudomanas, Acinetobacter* ve *Escherichia coli* gibi Gram negatif bakterilere karşı önemli antibakteriyel etki sergiledi. Burada, ılıman şartlar altında yüksek verimle kolaylıkla sentezlenebilen yeni potansiyel antibakteriyel maddeler bildirilmiştir. Ancak, bu üç bileşiğin daha ileri araştırmalarının ve *in-vitro* etkinlik testlerinin yapılması gerektiği açıktır.

Anahtar Kelimeler: Anti-bakteriyel maddeler, ilaç direnci, sistein, tiyazolidin-4-karboksilik asit

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Sorumlu Yazar

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Examination of antibacterial properties of three thiazolidine-4-carboxylic acid derivatives against *Pseudomonas, Acinetobacter, Staphylococcus aureus,* and *Escherichia coli*

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Abstract

Treatment of multi-drug resistant bacteria is a growing problem for global public health. The new active pharmaceutical ingredients are needed to keep up with the resistant. It is known that Thiazolidine-4-carboxylic acids (TCA) are able to inhibit bacterial growth by mimicking various essential functions of naturally occurring amino acids. Therefore, three TCA derivatives, two of them are novel, were aimed to synthesis, and their antibacterial activities have been investigated on multi-drug resistant (MDR) bacteria. Compounds (1a-c) were synthesized from L-Cysteine hydrochloride and dihydroxybenzaldehyde derivatives and their in vitro activities against multi-drug resistant bacteria were assayed by the Kirby-Bauer method according to CLSI criteria. 1a-c exhibited significant antibacterial effect against Gram-positive bacteria such as *S. aureus* and Gram-negative bacteria like *Pseudomanas, Acinetobacter,* and *Escherichia coli* superior to current antibiotics. Here, new potential antibacterial agents, which can be easily synthesized in high yield under mild condition, have been reported. But it is clear that further research and in-vitro activity tests of these three compounds should be performed.

Keywords: Anti-bacterial agents, drug resistance, cysteine, thiazolidine-4-carboxylic acid

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INTRODUCTION

Nitrogen-containing five-membered heterocyclic compounds are found in the structures of several natural products and pharmaceuticals. Most of them are used as synthetic intermediate products, reactants, ligands, or asymmetric synthesis catalysts.[1] Because their many synthesized derivatives are biologically active, thiazolidine has recently become an increasingly used heterocyclic system.[2,3] It has often been mentioned in previous studies that thiazolidine derivatives have antibacterial[4], anti-cancer[5,6], antiviral[7] and enzyme inhibitor[8] effects. Furthermore, thiazolidine-4-carboxylic acid (TCA) derivatives have been known as structural analogue of proline that is an essential amino acid for bacteria.[9]

Antibacterial resistance has become an increasing problem for all of the world.[10,11] Treatment options have nearly been exhausted for some bacteria such as *Pseudomonas spp, Klebsiella spp, Escherichia coli, Acinetobacter spp, Enterobacter spp,* and *Enterococcus spp.* Especially for treatment of nosocomial infection bacteria has become much more difficult. Shortly, in the present day, physicians need access to new antibacterial drugs much more than in the past.[12,13]

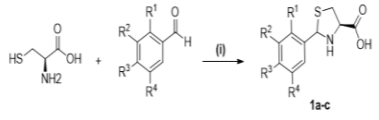
Our group has been working on the development of antibacterial materials for a long time.[14-17] Hence, we aimed to synthesize TCA derivatives and investigated their antibacterial properties on multi-drug resistant (MDR) bacteria. The result showed that TCAs have significant antibacterial activity on Gram-positive (*S. aureus*) and Gram-negative bacteria (*Pseudomanas*, *Acinetobacter*, and *Escherichia coli*).

MATERIALS and METHODS

All the chemical substances used for synthesis of compounds were provided commercially (Merck, Sigma-Aldrich, and Fluka). Melting points of the compounds were measured using an Electro thermal 9100 apparatus. ^{1}H and ^{13}C NMR spectra were recorded using a Varian 300 MHz Mercury Plus instrument using TMS as an internal standards.

Synthesis of TCA derivatives [18]

The benzaldehyde derivative (10 mmol) was dissolved in EtOH (10ml). To the solution was added L-Cysteine hydrochloride (1.57 g, 10 mmol) and NaOAc (0.98 g, 12 mmol) dissolved in water (10ml). The reaction mixture was then stirred for 24 hours at room temperature. The precipitate was then separated by filtration and washed several times with EtOH (Figure 1).



	R¹	R²	R³	R⁴
1a	OH	OH	H	H
1b	OH	H	OH	H
1c	OH	H	H	OH

Figure 1. Synthesis of TCA derivatives (**1a-c**). Reagents and conditions: (i) NaOAc, H_2O/EtOH, 24h, rt.

(*2RS,4R*)-2-(2,3-dihydroxyphenyl) thiazolidine-4-carboxylic acid (1a)

White solid, yield 95%, 2.29 g, mp 214-216 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δH 2.97 (dd, 1H, *J* 9.7, 10.0 Hz, N-CH_2-CH-CO_2H), 3.04 (dd, 1H, *J* 4.4, 10.5 Hz, N-CH_2-CH-CO_2H), 3.20 (dd, 1H, *J* 7.0, 9.4 Hz, N-CH_2-CH-CO_2H), 3.34 (dd, 1H, *J* 7.0, 9.7 Hz, N-CH_2-CH-CO_2H), 3.83 (dd, 1H, *J* 7.9, 7.3 Hz, N-CH-CO_2H), 4.22 (dd, 1H, *J* 5.9, 5.3 Hz, N-CH-CO_2H), 5.64 (s, 1H, S-CH-NH), 5.84 (s, 1H, S-CH-NH), 6.56-6.80 (m, 6H_{aro}).^{13}C NMR (75 MHz, DMSO-d_6) δc 37.7 (S-CH_2-CO_2H), 38.8 (S-CH_2-CO_2H), 65.4 (CH-CO_2H), 65.7 (CH-CO_2H), 66.5(S-CH-NH), 68.7 (S-CH-NH), 114.9, 115.6, 117.2, 118.7, 119.2, 119.5, 125.3, 128.7, 143.6, 144.3, 145.5, 145.9 (12C, aromatic), 173.2 (C=O, asit), 173.6 (C=O, asit).

(*2RS,4R*)-2-(2,4-dihydroxyphenyl) thiazolidine-4-carboxylic acid (1b)[19]

Beige solid, yield 92%, 2.22 g, mp>300 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δH 2.94 (t, 1H, *J* 9.1 Hz, N-CH_2-CH-CO_2H), 3.06 (dd, 1H, *J* 4.4, 10.2 Hz, N-CH_2-CH-CO_2H), 3.20 (dd, 1H, *J* 7.3, 10.0 Hz, N-CH_2-CH-CO_2H), 3.31 (dd, 1H, *J* 7.6, 9.1Hz, N-CH_2-CH-CO_2H), 3.76 (dd, 1H, *J* 7.6, 8.2 Hz, N-CH-CO_2H), 4.23 (dd, 1H, *J* 4.4, 6.4 Hz, N-CH-CO_2H), 5.57 (s, 1H, S-CH-NH), 5.75 (s, 1H, S-CH-NH), 6.17-6.33 (m, 4H_{aro}), 7.09 (d, 1H_{aro}, *J* 8.2 Hz), 7.11(d, 1H_{aro}, *J* 7.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ_c 37.7(S-CH_2-CO_2H), 39.0 (S-CH_2-CO_2H), 65.2 (CH-CO_2H), 65.8 (CH-CO_2H), 66.5 (S-CH-NH), 68.7 (S-CH-NH), 103.0, 103.4, 106.8, 107.1, 115.2, 118.0, 128.2, 126.6, 156.3, 156.9, 158.3, 158.9 (12C, aromatic), 173.3 (C=O, asit), 173.7 (C=O, asit).

(*2RS,4R*)-2-(2,5-dihydroxyphenyl) thiazolidine-4-carboxylic acid (1c)

White solid, yield 96%, 2.31 g, mp 217-219 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 2.97 (dd, 2H, *J* 9.1, 6.4, 10.0 Hz, N-CH_2-CH-CO_2H), 3.20 (dd, 1H, *J* 6.7, 10.0 Hz, N-CH_2-CH-CO_2H), 3.34 (dd, 1H, *J* 7.3, 9.7 Hz, N-CH_2-CH-CO_2H), 3.82 (dd, 1H, *J* 8.5, 7.3 Hz, N-CH-CO_2H), 4.16 (dd, 1H, *J* 6.0, 6.4 Hz, N-CH-CO_2H), 5.57 (s, 1H, S-CH-NH), 5.78 (s, 1H, S-CH-NH), 6.49 (dt, 2H_{aro}, *J* 15.5, 6.7 Hz), 6.59 (dd, 2H_{aro}, *J* 8.5, 9.1, 7.9, 6.1), 6.77-6.75 (t, 2H_{aro}, *J* 2.6, 5.3 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ_c 37.7(S-CH_2-CO_2H), 38.9(S-CH_2-CO_2H), 65.5 (CH-CO_2H), 65.7(CH-CO_2H), 66.4 (S-CH-NH), 68.3 (S-CH-NH), 113.4, 114.7, 115.1, 116.2, 116.3, 117.1, 125.2, 128.9, 147.7, 148.2, 150.3, 150.5, 173.2 (C=O, asit), 173.6 (C=O, asit).

Molecule properties such as geometrical structure, molecular orbital figures, HOMO and LUMO energies ionization potential, electron affinity, electronegativity, chemical hardness, chemical softness, and dipole moment were calculated using the Gaussian program and DFT/6-311+G(d,p) fundamental set (Figure 2).

Bacterial Strains

MDR bacteria isolated from the ICU (Intensive Care Unit) of Sakarya University between 2010

and 2015 and showing an explicit antibacterial resistant property were used in the study. Bacteria were stored -80 °C deepfreeze in skim milk. Prior to study, each strain was subculture on 5% blood agar at 37 °C for consecutive two days. From the MDR *Acinetobacter baumannii* strains yielded in the second passage, bacteria suspensions were prepared in tryptone soya broth (TSB) (Oxoid, Basingstoke, UK), and adjusted to a turbidity equal to McFarland 0.5 (1.5 x 108cfu/ml) (DIN EN 1040, 2005). All strains were studied with both quantitative suspension test and agar well disk diffusion method.

94 clinical isolate strains obtained from bacteremia blood specimens from hospitalized patients of multidrug-resistant *Acinetobacter baumannii*, *P. aeruginosa*, *E.coli* and *S. aureus* were examined. Bacterial origins and properties have been summarized in table 1.

Table 1. Properties of Study Bacteria

Bacteria[a]	n	Resistance pattern
Staphylococcus aureus	25	Methicillin resistant and susceptible isolates
Escherichia coli	20	Beta-lactamases positive isolates, ESBL positive
Pseudomonas aeruginosa	20	MDR isolates
Acinetobacter baumannii	29	MDR isolates
Total	**94**	

[a]Isolated from blood samples collected from ICU of Sakarya University.

Disk Diffusion Test

The antibiotic susceptibility profiles of all isolates were assessed by Kirby Bauer's disc diffusion method according to the recommendations of Clinical and Laboratory Standards Institute (CLSI).[20] Antimicrobial disks were obtained from Oxoid. 90-mm-diameter plates containing muller hinton agar at a depth of 4.0 mm were used for disk diffusion tests. The agar surface was inoculated by using a swab dipped in a cell suspension adjusted to the turbidity of a 0.5 McFarland standard. The inoculum and each the disks were allowed to dry.

4% wt. test material (**1a-c**) in Ethanol has been used. The plates were incubated in air at 36 °C, and the zone diameters surrounding the antimicrobial disks were read on 24 h.

Agar Well Diffusion Test

Each Mueller-Hinton agar plate was inoculated with the microorganism by streaking the swab over the entire sterile agar surface. This procedure was repeated by streaking 2 more times, rotating the plate each time to ensure even distribution of the inoculum. As a final step, the rimof the agar was also swabbed. Once the agar was solidified, it was punched with an eight millimeters diameter wells and filled with 50 µL of test materials (**1a-c**) in Ethanol.

RESULT AND DISCUSSION

The cyclisation reaction of L-Cysteine hydrochloride and benzaldehyde derivatives has

been used.[21,22] TCAs **(1a-c)** were obtained in high yields.[18] Tests were performed with different concentration rates of the **1a-c** (5 µg/ml; 10 µg/ml; 20 µg/ml; 30 µg/ml; 40 µg/ml; 50 µg/ml and 60 µg/ml) and the best result was obtained concentration of 40 µg/ml.

The thiazolidine derivatives were shown more maximum sensitivity than current antibiotics tested against the origins of *Staphylococcus aureus*, *Acinetobacter*, *E.coli*, and *Pseudomonas.* Even though the results are close together within three samples, it can be said that the efficiency order has decreased in sequence **1a ›1c ›1b** for Gram-negative bacteria and **1a ›1b ›1c** for Gram-positive bacteria (*Staphylococcus*). Average results of resistance against thiazolidines and calcic antibacterial have been summarized in table 2 and table 3.

Table 2. Mean Zone Diamaters for Gram-negative resistant bacteria

Sensitivity zone (mm)	n	1a	1b	1c	CAZ[a]	IMP[b]	GN[c]	AK[d]	LVF[e]	TZP[f]	SAM[g]	CIP[h]
P.aeruginosa	20	32	29	29	0	9	0	13	0	18	0	1
A.baumannii	29	33	29	31	1	4	12	11	0	1	0	0
E.coli	20	35	30	31	13	25	11	16	12	21	3	11
Mean Zone Diamater		**33**	**29**	**30**	**5**	**13**	**8**	**13**	**4**	**13**	**1**	**4**

[a]Ceftazidime; [b]Imipenem; [c]Gentamicin; [d]Amikacin; [e]Levofloxacin; [f]Piperacillin-tazobactam; [g]Ampicillin sulbactam; [h]Ciprofloxacin

Table 3. Mean Zone Diamaters for Gram-positive resistant bacteria *Staphylococcus aureus*

	1a	1b	1c	VAN[a]	TEC[b]	CIP[c]	ERT[d]	SAM[e]	GN[f]	CEF[g]	COT[h]
Mean Zone Diamater (mm)	33	31	27	16	16	20	17	18	17	14	17

[a]Vanomycin; [b]Teicoplaine; [c]Ciprofloxacin; [d]Erytromycin; [e]Ampicillin-Sulbactam; [f]Getamycine; [g]Ceftriaxone; [h]Co-Trimoxazole

A TCA contains thiazolidine and dihydroxybenzene groups. At the present time, a thiazolidine cycle is found in many drugs as the active materials. Furthermore, a TCA ring is separately used as mucolytic, hepatoprotectant, and antineoplastic.[23,24] Similarly, it is also known that dihydroxybenzene groups are biologically active and found in the structure of many drugs and natural products. For instance, 1,2-dihydroxybenzene, known as Catechol, composes the core of many natural products and drugs.[25,26] The 1,3-dihydroxybenzene (Resorcinol) and 1,4-dihydroxybenzene groups are the building blocks of several natural products.[27-30] For all these reasons, we think these compounds may use in humans. However, the requirement for many *in vivo* and *in vitro* tests for this process should be done.

CONCLUSION

It was determined that TCA derivatives have significant antibacterial activity for Gram-positive bacteria such as *S. aureus* as much as for Gram-negative bacteria such as *Pseudomanas*, *Acinetobacter*, and *Escherichia coli*. Although, they have similar antibacterial effects, **1a** exhibited the best result among them. Their energy properties are also similar with each other according to Gaussian calculation. However, **1a** has the highest dipole moment value. The antibacterial effect of **1a** may connect with this result. Additionally, differences in activities against Gram-negative and Gram-positive bacteria may be related to lipid absorption of molecules or optic density variations.

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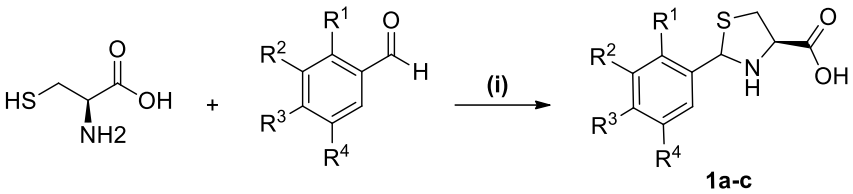
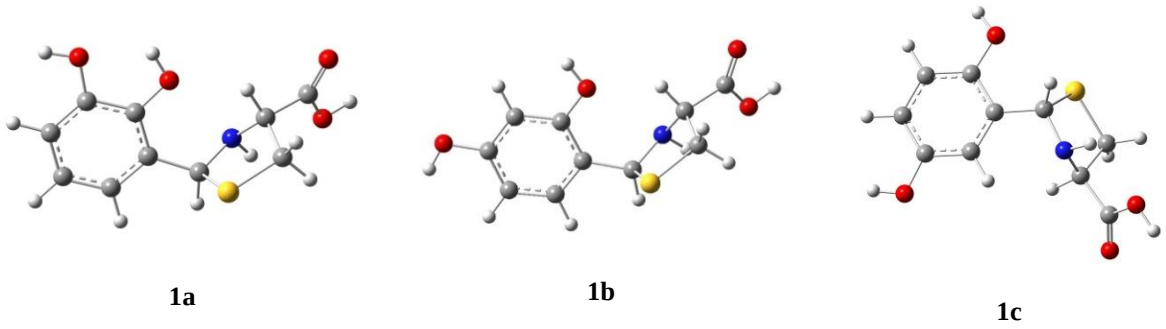


	R^1	R^2	R^3	R^4
1a	OH	OH	H	H
1b	OH	H	OH	H
1c	OH	H	H	OH

Figure 1. Synthesis of TCA derivatives (**1a-c**). Reagents and conditions: (i) NaOAc, H_2O/EtOH, 24h, rt.



1a

Energy: -1141,7497 a.u.

Dipole Moment: 2,5115 Debye

E_{HOMO} : -5,94446eV

E_{LUMO} : -0,57471 eV

$\Delta E_{HOMO-LUMO}$= 5,36974 eV

1b

Energy: -1141,7492 a.u.

Dipole Moment: 2,3842 Debye

E_{HOMO} : -5,94092 eV

E_{LUMO} : -0,49281 eV

$\Delta E_{HOMO-LUMO}$= 5,44811 eV

1c

Energy: -1141,7506 a.u.

Dipole Moment: 2,1924 Debye

E_{HOMO} : -5,69112 eV

E_{LUMO} : -0,61744 eV

$\Delta E_{HOMO-LUMO}$= 5,07368 eV

Figure 2. Calculated geometric structures of 1a, 1b and 1c using DFT method with 6-311G (d, p) basis set.

Table 1. Properties of Study Bacteria

Bacteria[a]	**n**	**Resistance pattern**
Staphylococcus aureus	25	Methicillin resistant and susceptible isolates
Escherichia coli	20	Beta-lactamases positive isolates, ESBL positive
Pseudomonas aeruginosa	20	MDR isolates
Acinetobacter baumannii	29	MDR isolates
Total	**94**	

[a]Isolated from blood samples collected from ICU of Sakarya University.

Table 2. Mean Zone Diamaters for Gram-negative resistant bacteria

Bacteria	**n**	**1a**	**1b**	**1c**	**CAZ[a]**	**IMP[b]**	**GN[c]**	**AK[d]**	**LVF[e]**	**TZP[f]**	**SAM[g]**	**CIP[h]**
P.aeruginosa	20	32	29	29	0	9	0	13	0	18	0	1
A.baumannii	29	33	29	31	1	4	12	11	0	1	0	0
E.coli	20	35	30	31	13	25	11	16	12	21	3	11
Mean Zone Diamater (mm)		**33**	**29**	**30**	**5**	**13**	**8**	**13**	**4**	**13**	**1**	**4**

[a]Ceftazidime; [b]Imipenem; [c]Gentamicin; [d]Amikacin; [e]Levofloxacin; [f]Piperacillin-tazobactam; [g]Ampicillin sulbactam; [h]Ciprofloxacin

Table 3. Mean Zone Diamaters for Gram-positive resistant bacteria *Staphylococcus aureus*

	1a	**1b**	**1c**	**VAN[a]**	**TEC[b]**	**CIP[c]**	**ERT[d]**	**SAM[e]**	**GN[f]**	**CEF[g]**	**COT[h]**
Mean Zone Diamater (mm)	33	31	27	16	16	20	17	18	17	14	17

[a]Vanomycin; [b]Teicoplaine; [c]Ciprofloxacin; [d]Erytromycin; [e]Ampicillin-Sulbactam; [f]Getamycine; [g]Ceftriaxone; [h]Co-Trimoxazole